Quick guide

The critical period

Frank Sengpiel

What is the critical period? Also known as the sensitive period, the critical period is a time during early postnatal life when the development and maturation of functional properties of the brain, its 'plasticity', is strongly dependent on experience or environmental influences. The concept of a critical period therefore plays an important role in the age-old nature *versus* nurture debate — to what extent are our abilities determined by intrinsic factors, such as our genes, or by extrinsic factors, such as childhood experiences? To be precise, there isn't a single critical period, but there are different critical periods for different brain functions, for example binocular vision or language acquisition.

How do we know there is a critical period? Most evidence comes from examples where the complete absence of certain experiences early in life prevents the development of associated brain functions. Later exposure to those experiences cannot make up for the earlier loss. Human 'feral children', such as Victor de l'Aveyron, Kaspar Hauser and, more recently, Genie, have provided insights in particular into the critical period for acquisition of the first language. But the extent of deprivation is usually not fully known, making the interpretation of any findings difficult.

In classical animal studies, sensory experiences have been withheld during various time windows in order to define critical periods for visual, auditory and somatosensory modalities. Perhaps the best-known example is that of 'monocular deprivation', pioneered by the Nobel laureates Hubel and Wiesel in the 1960s, in which suturing shut the lids of one eye throughout the critical period causes functional blindness in that eye, despite the fact that the retina of the deprived eye works fine after re-opening the lids. With regard to hearing, the development of an auditory space map in the midbrain has been studied extensively: it requires calibration by visual input because the input from the inner ear does not contain spatial information.

What starts the critical period? At a functional level, it seems that the various critical periods start very shortly after the relevant sensory information first becomes available: the critical period for 'ocular dominance' (the relative representation of the two eyes in the primary visual cortex) begins just after eye-opening in animals such as cats or ferrets which are born with closed eyelids, or at birth in species born with open eyes, like humans. Similarly, the onset of hearing marks the start of the critical period for binaural integration in the auditory brainstem.

At a cellular level, it has remained unclear until recently what changes occur in the brain so that it develops normally in the absence of sensory input one day but goes into decline the next day if that sensory experience continues to be withheld. For example, orientation maps in the visual cortex of young ferrets raised in complete darkness are close to normal up to five weeks of age, when ferrets' eyes open, but then disappear over the next few weeks if the animals are kept in the dark.

It now appears that a certain level of intracortical inhibition marks the onset of the critical period, at least in the visual cortex. The development of cortical inhibitory circuitry initially lags behind that of the excitatory circuitry. Of particular interest are the so-called large basket cells, which use the inhibitory transmitter γ-amino butyric acid (GABA). If their maturation is accelerated, such as in mice over-expressing the nerve growth factor BDNF, then the critical period for the effects of monocular deprivation on cortical ocular dominance starts (and ends) sooner than in normal mice. Conversely, dark-rearing delays the maturation of GABAergic transmission and the onset of the critical period and prolongs its duration. More direct evidence for the role of GABAergic neurons in the control of the critical period comes from mice deficient for an enzyme needed for the synthesis of GABA in presynaptic terminals. These mice are insensitive to monocular deprivation throughout life, but treatment with diazepam (which acts as a GABA agonist) restores cortical plasticity.

What ends the critical period? The critical period is characterized by changes not only at the level of synaptic transmission, but increasingly by structural changes, which result in closure of the critical period. In the visual cortex, changes in the composition of the NMDA receptor, which plays a key role in synaptic strengthening and weakening, have been linked to the type of visual experience an animal has had during the critical period, for example, whether it has been reared in a normal environment or in the dark. Depending on previous experience, these receptor changes are to some extent reversible, but as the critical period comes to its end, they make it harder for further synaptic plasticity to occur.

Recent advances in live imaging methods at the microscopic level have made it possible to visualize the dynamics of dendritic spines, the presumed site of synaptic plasticity. In the course of the critical period spine turn-over and motility decrease, their number and shape becoming more stable. Spine motility is controlled by tissue plasminogen activator (tPA), which declines

with age but is upregulated by monocular deprivation during the critical period. It appears that tPA is a permissive factor in cortical plasticity, but it does not determine whether new synapses will be formed or existing ones eliminated — this might instead depend on local levels of pre- and postsynaptic activity.

The most significant structural changes in the cortex towards the end of the critical period are those seen in the extracellular matrix, a network of macromolecules, which becomes more and more rigid during postnatal development. A major component of the extracellular matrix are chondroitinsulfate proteoglycans: these molecules aggregate in perineuronal nets, lattice-like structures that ensheathe in particular the GABAergic large basket cells implicated in the control of the critical period, leaving just small windows at the sites of synaptic contact and inhibiting axonal sprouting. It has been shown in adult rats that enzymatic digestion of chondroitinsulfate proteoglycans makes the visual cortex susceptible again to the effects of monocular deprivation, suggesting that the maturation of the extracellular matrix plays a key role in the closure of the critical period.

Another factor that appears to contribute to the closure of the critical period is an increase in the Nogo-66 receptor for the myelin-associated growth inhibitor Nogo. It in turn activates an intracellular pathway which regulates the actin cytoskeleton and thus controls axonal growth. Mice lacking this receptor exhibit visual cortical plasticity in response to monocular deprivation well into adulthood.

Is there plasticity beyond the critical period? Of course the critical period does not end abruptly one day, but a number of studies have now reported plasticity in the mouse visual cortex well beyond what would have been defined as the critical period. This sort of adult plasticity may or may not be based on the same molecular mechanisms as classical critical period plasticity. Also, earlier sensory experiences predispose the brain to rapidly respond again to similar experiences made later on, even in adulthood, and training is likely to enhance such adult plasticity. Probably more interesting still is the question whether one can somehow turn back the clock and put adult cortex into a plastic state equivalent to that during the critical period. This could be of great therapeutic significance if it allowed us to correct, in adulthood, things that went wrong in brain development during childhood. One such example is amblyopia, loss of visual acuity in one eye because of early ocular abnormalities, for which there is no treatment available in adulthood. A loosening of the extracellular matrix or a blockade of the Nogo-66 receptor are currently the most promising avenues of research. However, no-one yet knows whether increased cortical plasticity will have unwanted side-effects. Presumably, the relative stability of cortical circuitry attained by the end of the critical period is beneficial to the individual, at least under normal circumstances, and a loss of that stability may disrupt cortical function in unforeseen ways.

Where can I find out more?

Berardi, N., Pizzorusso, T., and Maffei, L. (2004). Extracellular matrix and visual cortical plasticity: freeing the synapse. Neuron *44*, 905–908.

Hensch, T.K. (2005). Critical period plasticity in local cortical circuits. Nat. Rev. Neurosci. *6*, 877–888.

Hofer, S.B., Mrsic-Flogel, T.D., Bonhoeffer, T., and Hübener, M. (2006). Prior experience enhances plasticity in adult visual cortex. Nat. Neurosci. *9*, 127–132.

Kacelnik, O., Nodal, F.R., Parsons, C.H., and King, A.J. (2006). Training-induced plasticity of auditory localization in adult mammals. PLoS Biol. 4:e71.

McGee, A.W., Yang, Y., Fischer, Q.S., Daw, N.W., and Strittmatter, S.M. (2005). Experience-driven plasticity of visual cortex limited by myelin and Nogo receptor. Science *309*, 2222–2226.

Philpot, B.D., Cho, K.K.A., and Bear, M.F. (2007). Obligatory role of NR2A for metaplasticity in visual cortex. Neuron *53*, 495–502.

School of Biosciences, Cardiff University, Cardiff CF10 3US, UK.
E-mail: SengpielF@cf.ac.uk

Essay

Flies' lives on a crab

Marcus C. Stensmyr and Bill S. Hansson

Although the ~3000 species belonging to the Drosophilidae family are customarily referred to as fruit flies — as for example *the* fruit fly, *Drosophila melanogaster* — many have essentially little to do with fruit. Most drosophilids feed on microbes, and can hence be found on a wide variety of substrates, of which some are quite peculiar. Arguably the strangest substrate inhabited by drosophilids is that of the three species that live on (and in) land crabs.

The first report of crab-living flies came from the distinguished entomologist Henry G. Hubbard (Figure 1A). In April 1894, Hubbard was invited to Montserrat (Figure 2A) by lime plantation owners who wanted his help in exterminating insect pests. Hubbard being a habitual insect collector naturally took

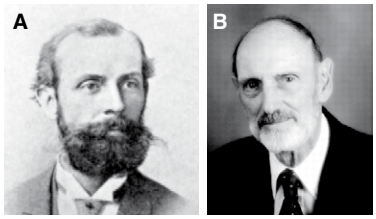

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Figure 1. Crab fly scientists.

(A) Henry G. Hubbard (1850–1899). According to newspaper clippings of his time "one of the most scientific entomologists in the United States", Hubbard was a pioneer in the field of insect pest control and an extensive insect collector. Hubbard was the first to report crab living flies. (B) Hampton L. Carson (1914–2004). *Drosophila* researcher par eminence, perhaps best known for his outstanding work on the Hawaiian drosophilid fauna. Carson rediscovered Hubbard's crab flies in 1963 and made the first detailed study on their biology. Carson later went on to discover two other fly species with the same odd host preference.